

ELAB GLP Subcommittee Executive Summary and Final Report Prepared for the July 28, 1997 Annual Meeting of ELAB

Summary:

In April of 1996 a Subcommittee of the Environmental Laboratory Advisory Board (ELAB) was formed to: 1) Characterize EPA Good Laboratory Practice (GLP) laboratory evaluation needs, 2) Evaluate alternatives to accreditation, 3) Examine implementation options, 4) Determine benefits of GLP accreditation to EPA and others, and 5) Determine how action by EPA would impact the Organization for Economic Cooperation and Development (OECD) programs and commitments. The Subcommittee developed 5 primary options for consideration by the ELAB: 1) Augment the current program and increase funds for the EPA monitoring program, 2) Develop a 3rd party accreditation system for GLP laboratories, 3) Increase the value of the current sponsor monitoring program, 4) Develop a process within the National Environmental Laboratory Accreditation Program (NELAP) to accommodate EPA GLP standards, and 5) Develop a registration list for EPA's Federal Fungicide, Insecticide, and Rodenticide Act (FIFRA) and Toxic Substances Control Act (TSCA) testing laboratories. A number of significant needs for intra-agency, interagency, and international harmonization as well as the impact of potential EPA action on these needs was developed. The cost of the current EPA GLP programs (including the quality assurance oversight effort) was found to be significant and undervalued by much of the regulatory oversight community (especially international regulators). The options developed by the Subcommittee will vary in cost and implementation complexity as well as their ability to address the various needs expressed in this report. It is clear that more resources should be made available to EPA's GLP monitoring and compliance program if these needs are to be met. However, the cost of adding these new resources must be balanced with the cost of the current program. Any new processes must be value adding and cost effective for the entire industry (regulators and regulated community) if these changes are to be successfully implemented. The international efforts to harmonize GLP programs and standards must also weigh heavily in any changes to the current program. The Subcommittee thinks their options provide for some interim relief to the current shortcomings and also offers suggestions for longer term improvements to the EPA GLP compliance monitoring program. The Subcommittee recommends that: 1) The GLP issue be disengaged from the current NELAP activity and timeline, 2) Interim relief be obtained by implementing the simpler aspects of key options outlined in this report, 3) The rule-making process be utilized to facilitate a long-term solution to the current problems, and 4) The entire regulated community be drawn into the review and comment aspect of possible solutions to ensure each facet of the new program is cost effective, value adding, and redundancy is minimized.

Background:

A series of Office of Inspector General (OIG) reports (1991-92) concerning EPA oversight of (GLP) laboratories that submit data to be used in Agency decision-making were very critical of the amount of auditing being done by EPA and the universe of facilities being audited. The report suggested that a 3rd party accreditation program might be a more effective way to manage the oversight responsibilities of the Agency. At this same time an effort was underway to create a National Environmental Laboratory Accreditation Program (NELAP) to set standards and normalize performance of environmental monitoring laboratories submitting data to the Agency as well as to many state and local decision-making bodies. In December, 1994 it was decided to include all organizations that submit data to EPA into the NELAP, including those regulated under the GLP standards of 40 CFR part 160 (FIFRA) and 40 CFR part 792 TSCA. As the GLP community began to interact with those developing NELAP, many questions were raised by representatives of the GLP community at the first National Environmental Laboratory Accreditation Conference (NELAC) in February, 1995. The Environmental Laboratory Advisory Board (ELAB), formed during 1995, was charged with the responsibility to advise EPA and NELAC concerning problem areas relating to the implementation of the NELAP program. Several ELAB subcommittees (including a GLP Subcommittee) were organized to examine specific work which needed to be done in order for NELAP to become fully functional. The ELAB GLP Subcommittee was formed during the first quarter of 1996.

On April 23, 1996 twenty-six individuals from different parts of the GLP regulated community, (private sector, EPA, USDA, FDA) met via telephone conference to discuss their ELAB GLP Subcommittee charter and begin a process of developing options for consideration by the ELAB (see Appendix A for the list of Subcommittee members). It was decided that basic to any option considered was the need to maintain the current GLP standards, to meet the needs of the interagency and international community, and be cost effective for members of the GLP regulated community. With this charge in mind the ELAB GLP Subcommittee divided into three sub-teams to address each facet of this charge. Team 1 was to look at options for the larger team to consider. They were also to examine the current EPA GLP compliance program and use this as a guide to bridge from present practice to potential options for the future. Team 2 was to look at the needs of intergovernmental agencies (EPA, FDA, etc.) and those of the international community. Team 3 was to develop information from a cost/benefit perspective which could be used to evaluate the cost effectiveness of the options selected and finally recommended to the ELAB.

On June 3, 1996 the ELAB GLP Subcommittee received a notice from the Environmental Monitoring Management Council (EMMC) of the EPA expanding the charter of the ELAB GLP Subcommittee to include looking at the GLP needs of all FIFRA and TSCA programs and to:

- Characterize the GLP laboratory evaluation needs of the Office of Prevention, Pesticides, and Toxic Substances (OPPTS) and the Office of Enforcement and Compliance Assurance (OECA).
- Evaluate feasible alternatives to NELAP accreditation.
- Examine program implementation options (e.g. NELAC, private sector, federal government).
- Determine the benefits of GLP accreditation to EPA and others.
- Determine how potential actions would impact Organization for Economic Cooperation and Development (OECD) programs and commitments.

The ELAB GLP Subcommittee integrated this expanded charter into the existing teams and began to address each of the areas of focus with the intent of preparing a final report and recommendations to the ELAB. Reports of the three teams of the Subcommittee are summarized in the following paragraphs.

Original Charter Team Summaries:

Team 1, Development of options and examination of current EPA GLP compliance program:

A list of laboratory evaluation needs was developed based on input from OPPTS and OECA representatives to the team (Appendix B). The laboratory evaluation needs are summarized as follows. Additional resources are needed to enable EPA to inspect over 2,000 laboratories generating data for EPA submission. The majority of the 2,000 identified laboratories actually participated in fewer than five submitted studies during the fiscal years 1993-1995 (these statistics are the most currently available). The current inspection program does not prioritize facilities by size or number of studies conducted. A means to identify the facilities generating data for EPA submission is needed. OECA currently relies on the OPPTS database of facility names and addresses taken from the cover pages of study reports. These names and addresses could be several years old since the work is often done long before the study report is submitted to the Agency for review. Timely evaluation of studies for which regulatory decisions are pending is desirable. OPPTS team members also indicated that it would be preferable to prioritize inspections of facilities with large numbers of studies underway as well as those performing long term and field studies. Persons performing the inspections should be capable of identifying technically meaningful issues and providing OPPTS with feedback regarding the importance of these issues. This list of needs also addressed issues raised by the 1991-1992 OIG reports. From this list of needs, Team 1 identified a set of 35 options which would meet various aspects of the OIG Report and also address the concerns raised around laboratory accreditation. Discussions with the entire Subcommittee concluded that several of these original options overlapped with certain aspects of other options, and eventually the option set was reduced to 5 which were then evaluated and developed further. The following is a general description of the final 5 options. A more detailed list along with implementation strategies, strengths, and weaknesses is shown in Appendix C of this report.

Option 1, Augmentation of the current program and increased funding and resources: The existing EPA OECA GLP compliance monitoring program would be continued but initially augmented in Phase I by redefining the universe of the facilities to be inspected with focus on facilities with study directors and primary/major data generators. Subsequently, the option could be expanded with increased funding in Phase II to increase the frequency of compliance monitoring so that sites could be visited in a more timely manner (2-3 years is the current international standard). Resources for the expansion in Phase II would come from one of three proposed sources: A) an increase in the EPA funds directed to the OECA, B) an increase in FIFRA registration fees could target funds for EPA to conduct GLP inspections, or C) funds could be obtained from an EPA OECA directed "GLP Inspection" fee. The increased frequency of compliance monitoring would be expected to increase the public confidence and international acceptance of the US EPA GLP programs.

Option 2, Third party accreditation for Good Laboratory Practice Standards: The development of a private third party accreditation program would be sanctioned by EPA for the purposes of inspecting and accrediting laboratories to GLP standards. Enforcement responsibilities would remain with the EPA. The program would include registration of laboratories, on-site inspections of the test site facility, along with technical and quality programs. A certificate would be issued for successful completion of the GLP compliance inspection, which would address international concerns and broaden market acceptance of the laboratory and data. This option could function as either a mandatory or a voluntary program depending on method of implementation

As the Accrediting Authority, the U.S. EPA OECA would establish a program to recognize third party accrediting organizations or bodies to provide laboratory accreditation to a GLP standard. Interested stakeholders, including third party accrediting bodies, sponsors, contract laboratories and others would help develop recommendations for the Program Description including: A) OECA's responsibility as the Accrediting Authority, B) Criteria for approving third party accrediting bodies, and C) Criteria for qualifying and training assessors.

Interested third party accrediting bodies would develop their GLP accreditation program based on these conditions. These programs would be reviewed by OECA who would sanction acceptable programs. Continued approval would depend on OECA's monitoring and periodic re-approval of the accrediting program. Accepted accrediting bodies could publicize their approval and existing GLP accrediting program, and begin to accept applications and complete the accreditation process as described.

Option 3, Increased value of sponsor monitoring programs: The existing EPA GLP Compliance Monitoring Program would be continued with the addition of recognition for sponsors' current and ongoing GLP inspection programs. Even though in the current program sponsors have full accountability for the quality and integrity of the data they submit to the EPA, the EPA has full responsibility for all aspects of compliance monitoring. In this option EPA continues their inspection/audit program in generally the same manner, but by recognizing current value in existing sponsors' GLP inspections of contract facilities, the OECA targeting scheme from the list of 2000-plus facilities would be altered. Sponsors (registrants) would have a new responsibility to report to the Agency each time they visited and evaluated a contract facility, preferably in an established electronic format.

EPA would retain the option to inspect any test site, but would prioritize their schedule to focus on regular inspections of sponsors, testing facilities with study directors and facilities generating the majority of the GLP data. By establishing a data base of sponsors' GLP inspections, EPA would be able to track the number of sponsors' inspections at sub-contracted test sites. Using this information, they would prioritize their need for inspections at remaining test sites that generate only a small amount of the data. By supplementing their inspection schedules with recognition of sponsor' schedules, the EPA would be much more effective in adequately scheduling inspection of testing facilities that generate the majority of the GLP data.

Option 4, NELAP accreditation for Good Laboratory Practice Standards: In this option the current federally-controlled EPA GLP Program, utilizing the current GLP standards, would be placed under the umbrella of NELAP as a parallel program and would operate independently of the other NELAP programs. Federal EPA inspectors would conduct priority GLP compliance inspections and data audits as well as participate in the activities of NELAC, with additional inspection support being provided by EPA approved third-party assessors.

The allocation of responsibilities would be as follows: EPA would continue to manage and direct the activities of the EPA GLP program, to maintain records derived from GLP study and laboratory evaluations, and to address both interagency and international harmonization, regulatory and compliance issues. NELAC would provide the administrative support for the accreditation program. Funding of the program would be largely derived from inspection fees levied by NELAC and/or third-party accrediting group(s) for accreditation inspections /assessments. In summary, NELAC would be responsible for facility accreditation while EPA would retain oversight responsibilities for the GLP Program.

Option 5, FIFRA/TSCA GLP Test Facility Registration: Facilities which intend to perform FIFRA and TSCA GLP studies for submission to EPA would be required to register their facility with EPA. Facility registration would involve an initial submission of information and documents from the facility for review to establish the basic profile for the facility. Documentation could possibly include: Description of size, organization, and capabilities of the facility; the organization, functions, and procedures of the quality assurance unit; general description of instruments and equipment used at the site, and the number and areas of expertise of staff. It might also include current list of standard operating procedures, resumes, CVs and training records of key personnel, floor plans of the facility, and a current master schedule. On a periodic schedule, facilities would be required to resubmit certain documents and information.

The Agency or a designated third party contractor(s) would audit the submitted documents. Registration would not confer approval. Facilities with corrected minor GLP deficiencies would be provisionally registered, while facilities with major GLP deficiencies would be targets for inspection. Periodic submission of the facility's master schedule would be required and would provide a means of monitoring work intended for submission to the Agency. This would allow OECA to prioritize its inspections and be able to conduct in-life audit reviews of on-going studies. To remain on the registration list, a submitter would need to continue to remain in GLP compliance verified by an EPA facility inspection audit.

Team 2, Interagency and international issues concerning laboratory accreditation:

U.S. Interagency Issues Pertaining to U.S. EPA Lab Accreditation - FDA Position Statement

Departments, Agencies and Administrations outside of the U.S. EPA potentially affected by a GLP accreditation program include the USDA program and the FDA GLP. While internally USDA does not have GLP requirements, USDA programs which collect and submit data to EPA in support of pesticide registration do require GLP compliance programs as part of their funding requirements. The FDA, on the other hand, has a well established GLP program. The outcome of the debate on developing a national GLP accreditation program has greatest impact on this program.

Since 1978, the FDA has had a program for inspecting GLP laboratories conducting non-clinical safety studies for pharmaceuticals, veterinary products, and medical devices program (frequency every 2-3 years). Such studies are conducted and reported in accordance with the GLP regulations found in 21 CFR part 58. There are currently no plans by the FDA to adopt an accreditation approach to regulate GLP laboratories. The program of inspections and data audits currently in place at the FDA provides the necessary level of data quality and integrity with minimal outlay of resources.

In developing its approach for regulating these laboratories, the FDA considered several options, including a third party accreditation program. The FDA concluded that a program of regular laboratory inspections and data audits, conducted by FDA personnel, was the most cost effective and efficient means to ensure the quality and integrity of data submitted to the FDA. The FDA reached this conclusion in part based upon its decision to include in the regulations a requirement that each laboratory appoint an independent quality assurance unit, as an internal monitoring process. This self-regulation approach was favored by the FDA as the least burdensome to industry and most efficient for FDA oversight. The advantages of the FDA approach to regulate non-clinical safety testing laboratories is recognized domestically and by other agencies of the U.S. government and internationally, including the EPA and OECD.

Implementation of an accreditation program by a third party would entail the added expenditure of resources to establish an infrastructure of training, oversight and additional regulations. There has been no information presented to the FDA at this point to suggest any justification for this added expense, nor does the FDA have any indication that its current program has been ineffective.

International Issues Pertaining to U.S. EPA and the OECD GLP Programs:

The development of a United States GLP standard by the FDA in the late 1970's prompted interest in GLP on the part of other OECD Member countries in order to ensure continued acceptance of their data in the large U.S. market. OECD's involvement flowed logically from a principle purpose of all of its programs--- the avoidance of non-tariff trade barriers between OECD Member countries as a consequence of national regulatory programs. It is frequently stated that the goal of the OECD program is the "international harmonization" of GLP requirements. In general, the OECD Member countries with national GLP programs have adopted the OECD Principles of GLP as the basic standard, as required by the 1981 Council Act. This is especially true for the 15 member states of the European Union, (whose standard is the OECD Principles verbatim), Japan (MHW, MAFF, MITI), the United States (FDA and EPA), and Switzerland. In general, there is a very high degree of harmonization amongst these countries. Newer programs based on GLP are being developed in Canada, Mexico and Brazil.

Equally relevant to analyzing the impact and conditions of a U.S. GLP accreditation program is the evaluation of existing bilateral agreements and MOU between the U.S. and OECD Member countries. These agreements reiterate provisions for meeting the Mutual Acceptance of Data Decision and goals, including promotion of data acceptance and reciprocity amongst participating countries, and continued cooperative relationship between countries. Requirements can be summarized into four general conditions: 1) Adherence to standards of GLP based on national GLP programs and the OECD Council Recommendations and Decisions; 2) Mutually consistent national programs, including periodic (approximately every two years) inspections by trained government inspectors, (or government sanctioned programs); 3) National compliance procedures, including notifying laboratories of observed deficiencies and requirements for corrective action; and 4) Periodically, providing the signatories with names and addresses of non-clinical health and environmental safety laboratories operating within the country and the dates of government or government sanctioned inspections, and current GLP compliance status.

None of these requirements either negate or promote the concept of developing a U.S. GLP Laboratory accreditation program. Critical, however, to evaluating the impact of accreditation on the U.S. EPA GLP program is the preamble to the document entitled "Revised Guide for Compliance Monitoring Procedures for Good Laboratory Practices." The preamble states that "Member countries will adopt GLP Principles and establish compliance monitoring procedures according to national legal and administrative practices..." Thus, it would appear evident that EPA could establish a third party accreditation program as long as EPA played an appropriate role in establishing and overseeing the program. This conclusion is consistent with programs already in place in several European countries.

Team 3, Cost/Benefit Analysis of Current Programs to Industry and Proposed Options:

A survey was developed and distributed to the EPA GLP community in an attempt to better understand the cost

of the current GLP regulations to the regulated community. This survey was conducted in an effort to determine the impact of GLP on the cost of research and to break-out the cost of the QAU as it monitors these programs. Approximately 900 Cost/Benefit Survey forms were mailed to members of SQA (400, members operating under EPA GLP regulations), NAICC (120), CSMA (300), and ACPA (~80). Organizations were to pool results into a single response for the entire organization. Fifty two responses were returned (sponsors, 16; Contract Labs, 14; Field Cooperators, 16; and others 6). The small response was insufficient to provide a reliable estimate of the total cost of GLP regulations to the industry. However, the cost of the QAU did provide some insight into the cost of the Quality Assurance portion of the GLP. The average cost of a QA professional from the companies represented in the survey was approximately \$70,000 per year (this cost would include benefits, travel, and QA program cost in addition to salary). Since there was a higher response of sponsors relative to independent QA respondents, this number may be an over estimate of the industry average, however it should not be drastically wrong. If this number is multiplied by the approximate 400 members of SQA associated with EPA programs, then it is clear that the current direct cost to industry for GLP QA programs approaches \$30 million annually. Additional indirect costs (i.e. archiving, training, etc.) drive this value even higher. This number becomes particularly significant when it is realized that the OIG Reports issued between 1991 and 1992 did not give any consideration/credit for the impact that EPA regulated industry QA programs have on data quality. The FIFRA and TSCA testing industry GLP QA program effort must be considered in whatever final decision is reached in the current oversight/monitoring debate if an acceptable cost effective revision is to be successfully implemented.

How the Options Address the Expanded Charter:

The charter of the Subcommittee was expanded by the EMMC at such a time (June 1996) that consideration was given to the new charter throughout the work of the Subcommittee. More detailed responses to the individual options relative to the expanded charter objectives are included in Appendix C. An overview of the findings relative to the individual aspects of the expanded charter are presented below:

Characterize the laboratory evaluation needs of OPPTS and OECA programs:

- ◇ Need to know who is currently doing the work (universe of laboratories). There are over 2000 laboratories currently supplying data for EPA review.
- ◇ Need to know when the work is being done. In-life audits are far more valuable and much less controversial than post-mortem findings. This is true both for determining the quality of the work being done and improving the quality for future work
- ◇ Need to know the level of compliance of the study during the data review phase, not after the tolerance has been set and a registration granted.
- ◇ Need for technically trained inspectors who can identify meaningful technical issues and assess their impact on the study (administrative problems are less of an issue than technical problems) and the review process.
- ◇ Need to have critical phase and timely ongoing audits for long-term studies.
- ◇ Absolute requirement for necessary resources to conduct timely audits and to provide reasonable monitoring oversight.
- ◇ Need to be able to balance work so heaviest data suppliers get reasonable oversight, but that all facilities are audited in a timely regular manner. This is particularly critical as international harmonization activities are increasingly changing the compliance arena.

Evaluate feasible alternative to accreditation: Three non-accreditation options were identified which would meet various aspects of the needs. They are:

- ◇ Augmentation of current programs and increased funding.
- ◇ Increased value for sponsor monitoring programs.
- ◇ Laboratory registration.

Examine program implementation options: Specific examples of how each of the options discussed would be implemented are discussed with the detailed option summary in Appendix C. There are general

issues which should be resolved no matter which option is ultimately selected. They are:

- ◇ Define the standard which will be used for the future monitoring program. This may be as basic as ISO vs. GLP standards, revised GLP standards to meet new OECD GLP Principles, or develop a new standard for an accreditation system (if necessary). The Subcommittee sees the greatest value in amending the current US GLP to meet the harmonization standard of the revised OECD GLP which should be issued later this year or early in 1998.
- ◇ Re-affirm the federal program basis for FIFRA and TSCA programs. This seems to go without saying, but continues to be a key part of the debate relative to NELAP.
- ◇ No matter which option or program is pursued in the future there may be a requirement for legislative changes to FIFRA and TSCA as well as amendments of the current EPA GLP standards to facilitate implementation of the new program.
- ◇ There will be a need to provide training and certification of new auditors who will be required to meet the expanded monitoring requirements.
- ◇ The resource for the overall program should be re-evaluated. If the current resources (dollars, manpower, and time) are not adequately meeting the needs, then they should be examined as part of the whole process. If new costs are to be added, every effort must be made to make certain there is not a redundancy in what is being done by the EPA and what is required by the industry. Each step must be value-adding.

Determine the benefits of accreditation to EPA and others: A detailed list of these benefits are presented in the discussion of Option 2 and 4 in Appendix C. Key items are listed here, detailed benefits and disadvantages are listed in Appendix C:

- ◇ Provides increased frequency of inspections, while allowing OECA to retain its authority and enforcement responsibilities
- ◇ Facilitates OECA's focus on data audits
- ◇ Provides an "approved" universe of laboratories
- ◇ Facilitates integration of regulatory and commerce issues, and streamlines administrative duties
- ◇ Meets international (OECD GLP) requirements
- ◇ Provides greater international acceptance of laboratory testing programs and data
- ◇ Financially self-sustaining, fee would be assessed to cover program cost

Determine how potential actions would impact OECD programs and commitments: The OECD GLP principles are being revised at the current time. It is expected that the new OECD principles should be issued later this year or early in 1998. These standards are geared to drive international harmonization of regulatory work and requirements. The US EPA GLPS will need to be amended if we are to meet the new international harmonization standards when they are finalized. The new standard will help determine the potential value of each of the options developed at this time.

Discussion:

In summary, the Subcommittee has developed five primary options for consideration by ELAB. These options (page 3, Appendix C) will vary in cost and implementation complexity as well as their ability to address various interagency and international needs expressed earlier in this document. Options 1 (Phase I), 3, and 5, will allow the Agency to augment the existing compliance monitoring program with minimal resource drain and added cost. But, the expectation is that these options, as stand alone options, are unlikely to meet all of the concerns of the international community, or the OIG comments concerning frequency of EPA GLP compliance monitoring. Additional resources (both manpower and capital) will be required in order to satisfy these more complex concerns. The decision tree depicted in Figure 1 identifies the Subcommittee's preference for consideration of alternative more comprehensive options, taking into account numerous relevant factors (complexity, cost, timing, value adding potential, and ease of implementation) that are expanded upon throughout this document.

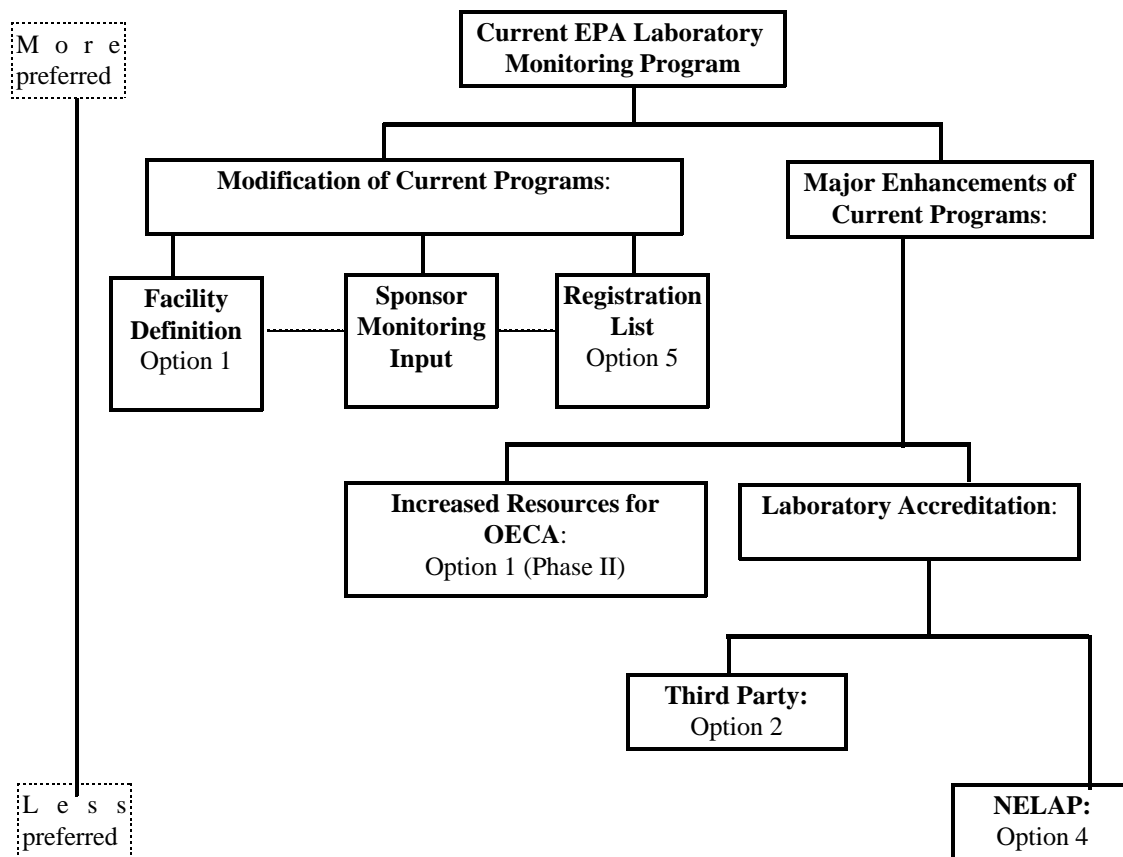
The ELAB should be advised that concurrent with this investigation of options to improve the current EPA GLP

Compliance Monitoring program are the efforts to harmonize the GLP Standards internationally through revision of OECD Principles of GLP followed by their adoption by OECD Member countries. This harmonization initiative is likely to impact to some degree the options identified in this report (particularly the larger, more comprehensive options 1 (Phase II), 2, and 4). Since the revision efforts are fairly close to being realized, it is recommended that decisions covering options 1 (Phase II), 2, and 4 be deferred until the new OECD GLP Principles are published and the harmonization activities are concluded.

Subcommittee evaluation of Options

Each of these options addressed different issues or concerns raised by members of the Subcommittee and an effort was made to consolidate various options into packages. Each of the options represented different approaches to meeting the needs (depending on the amount of time and resources to be applied to the problem. The options also spanned a number of potential activities which were very divergent in nature. Based on these considerations the Subcommittee concluded that the development of a decision tree view of the options (Figure 1) was more representative of their conclusions than reducing/condensing the primary option set further.

Figure 1. Decision tree view of an implementation scheme for the 5 options developed by the ELAB GLP Subcommittee.



The Subcommittee considered complexity, cost, timing, value adding potential, and ease of implementation and then through a multi-voting process concluded that options 1 (Phase I), 3, and 5 would be the easiest (fastest and least costly) to implement. The Subcommittee recognized that these three options by themselves or in combination were unlikely to address key international concerns such as frequency of auditing and/or certification. Option 1 (Phase II), notwithstanding the difficulty in obtaining additional funding, has the greatest potential of addressing the most needs with the least disruption and cost. Option 2 may require more resources to implement. There was

one overriding consensus within the Subcommittee and that was that option 4 was the least attractive of all the options because it posed the largest number of issues and constraints (see Appendix C). It is critical that any additional program cost be offset by value adding benefits to industry for any of these options to be implemented successfully.

RECOMMENDATIONS:

1. Disengage the GLP issue from the NELAP activity and timeline. There are too many potential problems with this option relative to other options notwithstanding the differences in program needs, resources, etc.
2. Focus immediately on implementing options 1 (Phase I), 3, and/or 5 to augment the current OECA compliance monitoring program. Should this modification in concert with harmonization efforts with the OECD GLP Principles still not address the perceived deficiencies of the OECA compliance monitoring program, thereafter, consider on a longer-term scale, the value to be added by implementing other options identified in this report.
3. Utilize the rule-making process to amend the US FIFRA/TSCA GLP standards to meet the new OECD Principles of GLP and for alignment with the many international harmonization efforts underway at the current time.
4. Utilize the rule-making process to include the entire regulated community in the review and comment discussion of possible solutions to ensure that each facet of the new program is cost effective, value adding, and redundancy is minimized.

APPENDIX A. Members of the ELAB GLP Subcommittee

David Alexander U.S. EPA	Maureen Barge FMC	Fran Dillon Stewart Pesticide Regis. Assoc.
David Dull (co-chair) U.S. EPA	Jimmy Flowers Dow Elanco	Debi Garvin Pacific Rim Consulting
Clive Halder Bayer Corporation	Louise Hess Lancaster Laboratories	Wynn John (co-chair) DuPont Ag Products
Robert Kiefer Chemical Specialties Mfrs. Assoc., Inc.	John D. Kobland American Cyanamid Ag Products Res. Div.	Francisca Liem U.S. EPA
Doris Mason Rhône-Poulenc Ag	Ray McAllister ACPA	John McCann McCann Associates
Chris Olinger U.S. EPA	Patricia O'Brien Pomerleau CIIT	Mick Qualls Qualls Ag Laboratory
Roxanne Robinson A2LA	Gary Roy Allied Signal, Toxicology	Patricia Royal Quality Systems Consultants, Inc.
Fred Siegelman U.S. EPA	Paul Swidersky Quality Associates, Inc.	Lee West RDA & NAICC
Tammy White USDA, Ag Exper. Station	Stan Woollen U.S. FDA	

Ad Hoc

Ted Coopwood EPA	George Fong Florida Environmental Admin.
John Henshaw Monsanto	Jeanne Mourrain EPA-AREAL

Appendix B. ELAB GLP SUBCOMMITTEE GROUP 1A SUMMARY REPORT

I. Goals

Study existing compliance inspection program
Gather additional statistics to define program
Characterize lab evaluation needs of OPPTS and OECA
Characterize lab evaluation needs of the Office of Toxic Substance
Characterize universe of U.S. labs subject to EPA GLP Compliance inspection program

II. Existing Compliance Inspection Program

A. Objective: For all data generated and submitted to EPA under FIFRA sections 3, 4, 5, 8, 18 and 24 and under sections 4 and 5 of TSCA,

- 1) assure that facilities conducting studies are in compliance with EPA GLP regulations;
- 2) assure that data submitted to EPA have been conducted in compliance with EPA GLP regulations;
- 3) assure the integrity, quality and validity of data that have been submitted.

B. Current Program Description - 1995 Data

1. Staffing - 17 full time equivalents (FTE), 11 which conduct inspections and audits. (Does not include FDA inspections)
2. Number of inspections performed - 82 (4 by FDA) OECA has no obligation to conduct a certain number of inspections. The number of inspections varies from year to year depending on the budget and other resources. There is no mandate for inspection of 100% of facilities.
3. Travel budget - \$100,000 currently. Historically, the travel budget has not been very good. Specific information was not released from OECA.
4. Outside contractors are not used.
5. OECA has determined that there are 2,000 facilities involved in data development for submission to EPA under GLP. Statistics provided for Fiscal Years 1993 - 1995 showed 3,040 facilities submitted data (Table 1). (Those 3,040 facilities were identified according to each data requirement, i.e. toxicology, efficacy, product chemistry, plant effects, animal effects, environmental effects, and residue chemistry. Therefore, a single laboratory could be counted more than once if it conducts studies in multiple disciplines.) 2,261 (74.4%) of the 3,040 facilities submitted 5 or fewer studies during that 3 year period (Table 2). 1,703 (56%) of the 3,040 facilities submitted 2, or fewer studies during that 3 year period.
6. OECA uses OPP and OPPTS databases for the laboratory list. The list of FIFRA laboratories will not be provided. A list of sponsor labs is not available at this time and will not be provided. A list of TSCA laboratories is not available at this time and will not be provided.

7. Each test site in a study is counted as a facility based on information provided in the final report by the sponsor. Facilities which are one-time field sites are included. A lab could be listed more than once if it conducts more than one discipline/ guideline. During 1993-1995, 1,195 or 39.3% of the facilities were involved in only 1 submitted study. The facility list includes a farmer's field as a field site if the sponsor's final report identified it as a field site. OECA prefers that sponsors not include farmer's fields if all of the work is done by the cooperator or sponsor.

8. OECA does not have the staff or budget to inspect all 2,000 facilities. Table 3 shows projections of budget and staff requirements to achieve inspection frequencies of 2, 3 or 5 year intervals. Even the longest interval (5 years) would require staffing and a budget of greater than 4 times the 1995 level.

9. As an outcome of criticism in an earlier report from the Office of the Inspector General, the current system does not target labs who submit most of the studies. This should be reevaluated in view of the current situation and the need to maximize effectiveness of resources.

OECA selects labs for inspection based on the following criteria:

- a. type of laboratory
- b. number of studies submitted to EPA
- c. type of studies submitted to EPA
- d. availability of inspectors
- e. availability of financial resources
- f. type of inspection (neutral scheme or for cause)
- g. geographical location (EPA regions)
- h. GLP compliance statement in the final report
- i. studies conducted after the promulgation of GLP
- j. laboratory participated in the study

10. OECA defines a study for inspection purposes using the same definition as given in the GLP regulations. Studies selected for inspection must have a valid GLP compliance statement and have been conducted after the promulgation of the EPA GLP. While EPA attempts to audit an entire study, this is not always possible when various facilities/sites are involved.

11. OECA uses OPPTS's databases for determining labs to be inspected. There is no other registration program for labs. The result is the lag time from when the laboratory starts developing data for submission to the time when studies are actually submitted and become known to EPA. (Re-registration requires progress reports, but new registrations do not).

12. The OECA compliance inspection program is supplemented by inspection/ monitoring done by QA Units of sponsor companies. This typically includes on- site inspection of each facility, protocol review, report review and, in some cases, data review. This is all in addition to the facility QAU monitoring specified in GLP.

III. Lab Evaluation Needs of OECA, OPPTS and Industry

A. OECA Priorities for the Lab Evaluation Program

1. There are no specific program requirements which must be satisfied. To inspect 2,000 labs according to the current program definition, additional resources are required as

listed in Table 3.

2. A means to accurately identify all facilities currently generating data for submission to EPA.

B. OPPTS Priorities for Compliance Inspections

1. Studies underway on chemical for which regulatory decisions are pending
2. Long term and field studies
3. Facilities with large numbers of FIFRA/FFDCA studies underway
4. Inspectors trained in conducting studies of the type they inspect to allow them to focus on meaningful violations and permit them to provide OPPTS information regarding the importance of problems observed

(Note Items III.B 1-3 require notification to OECA of ongoing study

schedules).

C. Toxic Substances Priorities for Compliance Inspectors

OTS did not respond on this issue.

D. Industry Priorities for a Compliance Inspection Program

1. Effective monitoring to assure data integrity
2. Added value for any program changes which result in increased costs to industry
3. Maintain GLP and QAU as an effective quality management program
4. Acknowledge industry monitoring of contract facilities
5. Reevaluate number and types of labs that need inspection to maximize utilization of resources. Justify decisions as business must do.
1. Minimize financial burden on small businesses by avoiding duplicative programs
7. Have adequate inspection (compliance monitoring) process to meet international needs.

TABLE 1

1. Expand goals to include characterization of labs/facilities and characterization of labs evaluation needs of Toxic Substances Office.

[Facility Analysis, Francisca Liem
Studies submitted FY 1993 - 1995
(OPPTS Pesticide Assessment Guidelines)]

Types of FIFRA laboratories

Types	No. Facilities	(%)	No. Studies	(%)
Toxicology	724	(24%)	11,696	(57%)
Product Efficacy	303	(10%)	1,536	(8%)
Product Chemistry	465	(15%)	1,675	(8%)
Effect on Plant	225	(7%)	700	(3%)
Effect on Animals	152	(5%)	437	(2%)
Effect on Environment	419	(14%)	1,570	(8%)
Research Farm	23		49	
Field Cooperator/Consultant	91		425	
University	25		83	
Foreign establishment	84		1,008	
Laboratory	143		1,398	
Domestic Government	48		606	
Miscellaneous	5		5	
Residue Chemistry	752	(25%)	2,841	(14%)
Research Farm	111		350	
Field Cooperator/Consultant	222		2,068	
University	78		211	
Foreign establishment	100		498	
Laboratory	210		2,551	
Domestic Government	29		41	
Miscellaneous	3		6	

TABLE 2
[Facility Analysis (Studies) FY93-95]

No. of small laboratories (based on no. of studies submitted in the last 3 years)

No. Facilities	# Studies	No. Facilities	# Studies
Toxicology		Product Efficacy	
262	1	138	1
118	2	58	2
60	3	22	3
47	4	24	4
28	5	4	5
<i>Total 515 (1-5 studies)</i>	<i>71%</i>	<i>246 (1-5 studies)</i>	<i>81%</i>
Product Chemistry		Effect on Plants	
172	1	102	1
90	2	29	2
36	3	23	3
26	4	18	4
19	5	10	5
<i>Total 343 (1-5 studies)</i>	<i>74%</i>	<i>182 (1-5 studies)</i>	<i>81%</i>
Effect on Animals		Environmental Fate	
63	1	165	1
26	2	64	2
12	3	35	3
8	4	25	4
7	5	22	5
<i>Total 116 (1-5 studies)</i>	<i>76%</i>	<i>311 (including field sites)</i>	
		<i>(1-5 studies)</i>	<i>74%</i>
Residue Chemistry			
293	1		
123	2		
58	3		
43	4		
31	5		
<i>Total 548 (including field sites)</i>			
<i>(1-5 studies)</i>	<i>73%</i>		

Small laboratories (submitted 1-5 studies in the last 3 years) is 74% of the total FIFRA GLP lab universe.

TABLE 3

Projected OECA Requirements of the GLP Inspection Program

Frequency of inspections	No. inspections per year	No. EPA staff	Travel budget
2 years	1000	160 (\$12M)	\$1,000,000
3 years	700	120 (\$9M)	\$ 770,000
5 years	400	68 (\$5.1M)	\$ 400,000

Appendix C. Detailed description of options developed for ELAB consideration by the ELAB GLP Subcommittee

OPTION 1 - EXISTING EPA FIFRA AND TSCA GLP COMPLIANCE MONITORING PROGRAM WITH AUGMENTATION (Phase I) AND INCREASED FUNDING (Phase II)

INTRODUCTION:

The current EPA FIFRA and TSCA Good Laboratory Practice (GLP) compliance monitoring program is a well-established, effective, nationally and internationally recognized program for monitoring scientific research. It is designed to assure the quality and integrity of GLP studies conducted in the laboratory or in the environment to support the safety and, in some cases, the efficacy of products. Key elements and problems of the current EPA GLP program are:

Elements:

- EPA Office of Enforcement and Compliance Assurance (OECA)/Office of Compliance (OC) conduct periodic on-site inspections and data audits of facilities for GLP compliance
- The archive and retention requirements are included for all completed GLP studies
- A considerable amount of monitoring and inspecting is performed on studies conducted under the GLP. In addition to the EPA OECA GLP compliance monitoring program, an independent Quality Assurance Unit (QAU) is required to continually monitor each study for GLP compliance and keep study management apprised of GLP compliance issues. QAU informs study management of the need for corrective action, if appropriate, through confidential QAU inspection reports. The QAU review may include commenting on each GLP study protocol. QAU always monitors/inspects at least one, and often many, "critical" phases of each GLP study. QAU routinely reviews each GLP study final report and accompanying data. The final report includes a list of QAU inspection and reporting dates for the study.
- For studies conducted under the GLP regulations, it has been estimated that approximately 20,000 final reports are submitted to EPA in a year. Therefore, it is possible that 60,000 independent QAU reviews could have been conducted on these studies conducted under the GLP. Additional sponsor monitoring and auditing may also be conducted on GLP studies sponsored out-of-house. Therefore, the estimate of possibly 60,000 reviews on studies conducted under the GLP regulations could be increased.
- Over 13 years of experience since the inception of the EPA FIFRA and TSCA GLP federal regulations have demonstrated that the quality and consistency of final reports submitted to EPA has greatly improved.

Problems:

- With the inclusion of field studies in the revised EPA GLP program over 8 years ago, the number of GLP laboratories/facilities identified by EPA for on-site inspections and data audits increased to over 2000.
- EPA OECA GLP on-site inspections do not currently focus only on the primary/major data generating facilities.
- One of the difficulties noted by the EPA's Office of the Inspector General (OIG) was that the frequency of EPA on-site GLP compliance monitoring of the laboratories/facilities was considered insufficient.
- The number of EPA OECA personnel who conduct GLP compliance inspections (initially 20 full-time equivalents, currently 11 full-time equivalents) and the funding resource is not currently sufficient to allow on-site GLP inspection frequencies to satisfy all constituencies, including those with international requirements.

DESCRIPTION OF OPTION:

The existing EPA OECA GLP compliance monitoring program is continued but initially augmented in Phase I by redefining the scope of the facilities to focus on the primary/major data generators. Subsequently, the option could

be expanded in Phase II to increase the frequency of compliance monitoring so that sites can be visited in a more timely manner (international standard is an audit every 2 to 3 years). The funds for the increased auditing frequency could be obtained from one of three proposed sources: A) an increase in the EPA funds directed to OECA, B) an increase in product registration fees with the extra fees directed to OECA conduct GLP inspections, or C) funds could be obtained from an EPA OECA directed "GLP Inspection" fee. The increased frequency of compliance monitoring by the EPA (or its designate(s)) will enhance public confidence and international acceptance of the US EPA GLP programs.

IMPLEMENTATION STRATEGY:

The current EPA GLP compliance monitoring program of on-site EPA inspections and data audits as well as independent QAU monitoring and inspecting for GLP compliance would continue. To initially augment the current program in Phase I, the scope and focus of the EPA on-site inspections would be redefined. The scope would be redefined to include facilities with Study Director(s). The focus of the EPA on-site GLP compliance monitoring would include facilities with study directors and primary/major data generating facilities. The option to visit all data generating facilities would be maintained. This redefinition could be implemented by EPA with a reasonable effort and within a reasonable period of time and would maximize EPA's effectiveness.

Funding increases suggested in Phase II should be directed to the EPA OECA GLP compliance monitoring program. The funds could be obtained directly from: A) the EPA budget, B) from an increase in the FIFRA or TSCA petition registration fees, or C) from a "GLP Inspection" fee. In all these cases, legislative approval and implementation time would be required. These additional resources would allow OECA to increase the frequency of compliance monitoring audits and to come into alignment with international audit frequency (currently international facilities receive a regulatory audit every 2-3 years).

STRENGTHS:

- This option preserves the integrity, structure and harmonization of the GLP international standards. The federal government's officials from EPA would continue to conduct on-site GLP compliance monitoring. This option should meet the perceived needs of EPA, FDA, industry, and the international OECD GLP community and not interfere with harmonization agreements with FDA. Because EPA conducts the GLP compliance monitoring inspections, the GLP facility would be provided with fair enforcement practices and removal/minimization of perceived conflict of interest and confidentiality issues. With a reasonable effort, EPA could initially augment the current OECA GLP compliance program's resource utilization by redefining the GLP facilities, and focusing inspections on the primary/major data generating facilities. This Phase I approach would provide consistency with the international GLP community's current revision efforts on redefining GLP facilities.
- The subsequent expansion of the option (Phase II) with increased directed EPA OECA funding has a primary benefit of providing EPA with expanded GLP inspection capabilities. This may provide a mechanism and increased capabilities for EPA to audit scientific safety data prior to final product assessment by OPPTS. The registration petition review process could potentially be accelerated and therefore provide an offset benefit and 'value-added' to the registrant. The additional directed funding will help offset current EPA OECA resource constraints. This approach should satisfy the requirements of all constituencies, including those with international requirements. It may serve as a national and international benefit enhancing the national confidence and international acceptance of the US EPA GLP compliance monitoring program.

WEAKNESSES:

- By redefining the GLP facilities and focusing on-site inspections toward the primary/major data generating facilities (Phase I), the frequency of EPA on-site inspections of some test sites may be reduced. This concern may be overcome by establishing a feedback mechanism between EPA and the regulated community.
- The expansion of the option (Phase II) with directed funding, the long term benefit of increasing the number of GLP facilities inspected by EPA will outweigh the time constraints for legislative authorization and

implementation. It may involve additional cost to EPA, the registrant, or the GLP facility. If funding is increased from a registration or "GLP Inspection" fee, a fair and equitable fee structure will have to be established. Testing facilities or sponsors with no international needs could be jeopardized by these fees and sponsor's may bear an unfair share of the costs. This could result in higher cost of already-expensive GLP studies without added value on the integrity and quality of data. It could potentially drive studies out of the US for cost reasons, impose a non-tariff trade barrier, and be an unnecessary burden for small highly specialized businesses.

CONCLUSION:

Adequate and appropriate monitoring, performed by qualified EPA inspectors, of scientific research laboratories conducting FIFRA and TSCA studies under the GLP regulations is of paramount importance to the regulated community, the international community, and, ultimately to the public. This option maintains the integrity of the EPA GLP compliance monitoring program, including the QAU GLP compliance monitoring. National and international GLP program harmonization is maintained. With a reasonable effort in Phase I, program augmentation through redefinition and focus could enhance the effectiveness of the current GLP compliance monitoring program. The increased funding for expansion of the option in Phase II will result in increased EPA GLP inspection capabilities and frequencies, meeting the needs of EPA, including the OIG, FDA, the industry and the international community. This expanded option has the potential to enhance the EPA registration petition review process. Directed funding resources may require time for approval and implementation but will result in increased EPA GLP compliance monitoring capabilities. With this option, EPA remains as the GLP compliance monitoring entity.

Option 2: THIRD PARTY ACCREDITATION FOR GOOD LABORATORY PRACTICE PROGRAMS

INTRODUCTION:

In 1994, the OECD GLP Panel issued a statement on GLP accreditation programs. Here, the OECD acknowledged the quasi-accreditation programs, and stated that such programs must be based on OECD GLP Principles and not ISO Guide 25, and have government oversight. For these reasons, this accreditation option is based on GLP standards, with the U.S. EPA having primary control and acting as the Accrediting Authority.

DESCRIPTION OF THE PROGRAM:

The development of a private third party accreditation program would be sanctioned by EPA for the purposes of inspecting and accrediting laboratories to GLP standards. Enforcement responsibilities would remain with the EPA. The program would include registration of laboratories, on-site inspections of the test site facility, along with technical and quality programs. A certificate would be issued for successful completion of the GLP compliance inspection, which would address international concerns and broaden market acceptance of the laboratory, and data.

As the Accrediting Authority, the U.S. EPA Office of Enforcement and Compliance Assurance (OECA) would establish a program to recognize third party accrediting organization or bodies to provide laboratory accreditation to a GLP standard. Interested stakeholders, including third party accrediting bodies, sponsors, contract laboratories and others would develop the Program Description; including:

- OECA's responsibility as the Accrediting Authority
- Criteria for approving third party accrediting bodies
- Criteria for qualifying and training assessors.

Interested third party accrediting bodies would develop their GLP accreditation program based on these conditions. These programs would be reviewed by OECA and sanction acceptable programs. Continued approval would

depend on OECA's monitoring and periodic re-approval of the accrediting program. Accepted accrediting bodies could publicize their approval and existing GLP accrediting program, and begin to accept applications and complete the accreditation process as described.

ACCREDITING PROCESS:

The accrediting process would begin upon submission of a completed application and fees for accreditation by the laboratory to the accrediting organization. After initial review, the accrediting organization would contact the laboratory to acknowledge receipt of the application and to discuss the assignment of trained assessors.

The object of the assessment is to determine whether or not a laboratory complies with the GLP requirements for accreditation, and can competently perform the types of tests for which accreditation is sought. At the direction of OECA, data audits of selected studies could also be performed. The assessor would close the on-site portion of the assessment with an exit briefing.

A written report of the assessor's findings, including any deficiencies or items needing corrective action would be reviewed at the exit briefing and left with the laboratory. If deficiencies are cited, the laboratory must submit a written plan of corrective action, with anticipated dates of completion. The accrediting body would review the corrective action for completeness. The inspection report, along with any corrective action would be sent to the accrediting review panel for a decision on accreditation. Once accreditation is approved, the laboratory would be issued a certificate by the accrediting body. A copy of the laboratory certificate and scope of accreditation is provided to OECA.

STRENGTHS:

- Provides increased frequency of inspections, while allowing OECA to retain its authority and enforcement responsibilities
- Facilitates OECA's focus on data audits
- Provides an "approved" universe of laboratories
- Facilitates integration of regulatory and commerce issues, and streamlines administrative duties
- Meets international (OECD GLP) requirements
- Provides greater international acceptance of laboratory testing programs and data
- Financially self-sustaining

WEAKNESSES:

- Additional cost to participating laboratories
- Perceived internal management focus away from internal QAU
- Confidentiality of proprietary information

CONCLUSION:

The development of a third party accreditation program for GLP promotes the use of the GLP standards which ensures continued OECD harmonization and international acceptance of data. Reliance on third party accreditors fosters increased inspection frequency and addresses concerns of the Inspector General and international community. Control is maintained by U.S. EPA, as the Accrediting Authority and Enforcement Entity. This program would most likely be accepted internationally. The currently anticipated accreditation costs appear reasonable and time to implement the program would be minimal.

OPTION 3: INCREASED VALUE FOR CURRENT SPONSOR MONITORING PROGRAMS:

INTRODUCTION:

The current EPA list of facilities generating GLP data is over 2000 facilities, and the EPA does not have adequate staff and resources to inspect them all on a regular schedule. This list is generated by listing study testing facilities plus all sub-contracted test sites identified in the final reports of studies conducted under the GLP regulations. Based on information from Francisca Liem of the EPA, the majority of these test sites generate only a small amount of the data. Currently, the EPA does not prioritize their inspection schedule to focus on facilities that generate the majority of the GLP data.

In addition to Agency inspections, sponsors also inspect their subcontracted test-sites for GLP compliance. FDA and EPA GLP regulations both assign sponsors (registrants) the responsibility for GLP compliance of a study, regardless of where the study is conducted. In response to this requirement, sponsors have developed GLP inspection programs for their contract facilities. Sponsors must attest to the GLP compliance of the entire study, including work conducted at sub-contracted test sites, when a study is submitted to the Agency. This responsibility was reinforced by EPA's Enforcement Response Policy, where monetary fines and penalties for noncompliance with GLP are much greater for sponsors that submitted studies than for contract facilities that conducted studies.

DESCRIPTION OF OPTION 3 - SPONSOR MONITORING PROGRAM:

The existing EPA GLP Compliance Monitoring Program is continued with the addition of recognition for sponsors' inspection programs. The EPA retains full responsibility for all aspects of compliance monitoring and continues their inspection/audit program in generally the same manner. By recognizing value in sponsors' GLP inspections of contract facilities, their targeting scheme from the list of 2000-plus facilities would be altered. Sponsors (registrants) would have a new responsibility to report to the Agency each time they visited and evaluated a contract facility, preferably in an established electronic format.

EPA retains the option to inspect any test site, but would prioritize their schedule to focus on regular inspections of sponsors, testing facilities with study directors and facilities generating the majority of the GLP data. By establishing a data base of sponsors' GLP inspections, EPA would be able to track the number of sponsors' inspections at sub-contracted test sites. Using this information, they would prioritize their need for inspections at remaining test sites that generate only a small amount of the data. By supplementing their inspection schedules with sponsor' schedules, the EPA would be much more effective in adequately inspecting testing facilities that generate the majority of the GLP data.

IMPLEMENTATION STRATEGY:

Sponsors would report their GLP compliance inspection schedules of contract facilities to the EPA, preferably in a established electronic format. Information reported would be standardized and include the date(s) of visit(s), length of visit, systems and types of operations observed, and pertinent information other than inspection findings. As described under "Inspection of a testing facility" in the GLP Standards, the "Quality Assurance Unit records of findings and problems, or to actions recommended and taken," would not be provided to the EPA.

EPA would then incorporate this information into a database. EPA would focus their inspection/audit resources first on sponsors, testing facilities with study directors and facilities generating the majority of the GLP data. Presuming a laboratory/test site that generated a small amount of data was evaluated with some regularity by sponsors, it would not routinely be inspected by EPA for GLP compliance, though they retain the option to do so at any time. If a test site was not visited regularly by multiple sponsors, presumably that test site would be targeted for inspection. Another factor influencing the number of inspections required would be the geographical location and crop setting that a field station conducted. Minor use type field laboratories (minor crop in an isolated local) would require less monitoring than a heavily used field or chemical analysis laboratory (major crop in the heart of a major use/production area.)

STRENGTHS:

- Sponsors have already invested in monitoring programs for contract facilities because they are responsible and liable for compliance at these facilities. By recognizing the value of sponsor's inspections as a supplemental part of the EPA GLP Compliance Monitoring program, their inspection/auditing schedule would be greatly enhanced. EPA can prioritize and balance their inspection resources to focus on facilities generating the majority of data and where there are suspected or obvious problems.
- Costs associated with this Option would be minimum for both EPA and sponsors because it utilizes existing programs. The sponsor reporting process will result in a minor increase in cost to GLP regulated community and potential cost-benefit.
- Quality of GLP data remains high because the integrity of existing programs does not really change. (Under the existing program, the quality of data has been considered good. The concern has been with the number of facilities and not being able to schedule EPA inspections on an acceptable frequency.)
- EPA's inspections are the primary enforcement-type inspections and overall control of GLP compliance resides with EPA. It is an important advantage because GLP are a federal regulation and primary responsibility for monitoring compliance must reside with EPA's Office of Compliance (OC). EPA's inspectors have the necessary background and experience with GLP to provide industry with fair enforcement practices and compliance assistance.
- The information required for EPA to effectively monitor sponsors' inspection programs is available to them under the current GLP regulation [160.35(c)]. A testing facility's written procedures for conducting inspections and audits are evaluated during EPA inspections, as well as training records for QAU personnel. Under existing GLP regulations, records of inspections conducted by a QAU (not the results) are available to representatives of the EPA or FDA. If the EPA finds that a testing facility's QAU procedures are not adequate during an inspection, they could cite them as findings in their GLP inspection report.
- EPA is not dependent on the quality of the inspections of any one sponsor. By establishing a data base for sponsors' inspections, the EPA would know how many sponsors have inspected a testing facility and how frequently the facility had been inspected. The Inspector Generals report stated that GLP facilities were not adequately inspected and OC did not have the resources to monitor so many test sites, but it did not take in to account or evaluate the on-going GLP monitoring of contract facilities by sponsors. Because of sponsor's liability and EPA's Enforcement Response Policy, U.S. testing facilities likely have undergone more GLP inspections than any place in the world.
- With a data base of sponsor's inspections, the EPA would know the identity of facilities actively conducting studies under GLP regulations. Currently, this information becomes available after the work has been completed and the final report has been submitted to EPA.

WEAKNESSES:

- There is a potential conflict of interest by allowing sponsors to watch over the contract test sites who are conducting the studies for them. Some sponsors may not be diligent in their assessment of the test sites, and may just do a cursory evaluation. Even if the program was conducted properly, the public's perception of this program may have negative connotations.
- If a contract lab thought that it would be unlikely that the Agency would inspect it (because it was visited by its clients), it may only meet the minimum standards required to keep its clients.
- International concerns about a "Certificate" of GLP compliance are not addressed.
- No provision to gather non-GLP compliance information if a sponsor chooses not to report it. The frequency of auditing may be misleading in reflecting a labs qualification to do GLP work.
- No other country uses sponsor auditing as a measure of GLP compliance or as an augmentation to Agency monitoring systems.

CONCLUSION:

Option 3 - Sponsor Monitoring Program depends on the continuation of EPA's GLP Compliance Monitoring Program. Implementation would be simple and cost effective because it utilizes the existing GLP compliance monitoring inspection programs of EPA and industry. EPA would prioritize their inspection schedule to focus on

facilities generating the majority of data and where there are suspected or obvious problems. Their program would be supplemented with a data base of sponsor's GLP inspections of contract facilities. Sponsors would only have added reporting responsibilities. The Agency start-up and maintenance costs for a data base would be minimized by the added benefits of prioritizing their inspection schedules.

The Option is in conformance with existing GLP regulations so there are no legal ramifications. Sponsors have primary responsibility for GLP compliance when studies or phases of studies are performed at contracted facilities. This Option should not present a conflict with FDA regulations or International Agencies. Under FDA GLP, sponsors also have responsibility to monitor their contract facilities. International Agency inspections have been primarily directed at testing facilities with study directors, but are now starting to inspect testing sites (without study directors).

Option 3 could be combined with Option 1 to augment the existing EPA Compliance Monitoring Program and/or with Option 5, a registration list program to facilitate tracking of facilities and test sites conducting GLP studies.

OPTION 4- INCLUSION OF GLP PROGRAM UNDER THE UMBRELLA OF NELAP:

GENERAL DESCRIPTION:

In this option the federally-controlled EPA GLP Program, utilizing the current GLP standards, would be placed under the umbrella of NELAP as a parallel program and would operate independently of the other NELAP programs. Federal EPA inspectors would conduct priority GLP compliance inspections and data audits as well as monitor the activities of NELAC, with additional inspection support being provided by EPA approved third-party assessors.

The allocation of responsibilities would be as follows: EPA would continue to manage and direct the activities of the EPA GLP program, to maintain records derived from GLP study and laboratory evaluations, and to address both inter-agency and international harmonization, regulatory and compliance issues. NELAC would provide the administrative support for the accreditation program. Funding of the program would be largely derived from inspection fees levied by NELAC and/or third-party accrediting group(s) for accreditation inspections /assessments. In summary, NELAC would be responsible for facility accreditation while EPA would retain oversight responsibilities for the GLP Program.

STRENGTH OF OPTION:

- Inspection fees collected by NELAC could provide additional manpower and funding to OECA
- As long as no changes are made in the GLP Standards to accommodate NELAC, the GLP harmonization efforts with FDA would not be disrupted, thereby retaining a single national GLP Standard
- Could increase frequency of inspections and possibly result in a certificate of accreditation which would be acceptable to the international community
- Established GLP trained third-party assessment/compliance group(s) could assist EPA in laboratory evaluations
- The EPA GLP Program under NELAC umbrella would provide a process by which EPA could use approved for-fee third party assessment groups without receiving funds directly from the regulated community
- Some laboratories, particularly contract laboratories, may derive a business incentive to becoming accredited

WEAKNESSES OF OPTION:

- Would need to resolve placing a federally mandated GLP program under a voluntary state program

- Would subject NELAC to intense criticism and challenges if the regulated community was not allowed in the NELAC constitution to impact NELAC activities/standards during their rule making procedures by using comment periods and public hearings, etc.
- International and inter-agency acceptance for the program could be jeopardized if the GLP Standards, or the harmonization efforts, are changed to accommodate NELAC
- Would need to resolve EPA delegating specific GLP Compliance Program responsibilities to states
- Would need to establish procedures for processing federal enforcement actions resulting from state and third- party evaluations/inspections
- Could require states to become involved in sharing oversight workload, training, and the development of enforcement cases for the GLP program with little incentive for the states
- Would require harmonization between US and international accreditation programs so as to not place US businesses at a competitive disadvantage
- Might not accommodate OPPTS needs to have appropriately timed audit information
- Provides little incentive for OECA to streamline/improve existing program
- Would provide the regulated community little “value added” impact for increased cost of accreditation
- Unless program is adjusted to make allowances for the number of facilities inspected, frequency of inspections, timeliness of reporting and quality of scientific reviews, stakeholders would receive little benefit from the increased number of facilities inspected
- Small specialty laboratories might be adversely affected by increased cost
- Accreditation will increase cost of testing in the US which might drive some laboratories out of the country
- Would need to establish procedures for EPA to direct third-party for-fee inspections/assessments
- Would need to establish appropriate and reasonable fee structures throughout the program
- Would need to provide OECA with additional resources to monitor the activities of NELAC and third-party groups, to provide appropriate training, scheduling and tracking inspections, archiving and processing inspection findings

CONCLUSION:

The EPA GLP program could be placed under the umbrella of NELAP if it were treated as a separate and independent program so as to not interfere with the success of the current Federally mandated GLP monitoring and compliance program. The additional resources that could be provided to the EPA GLP program by the states or third- party assessment group(s) could be used to increase the responsiveness of the Agency’s GLP program, however, ownership and control of the program would be very cumbersome in this dual oversight system. By not changing the GLP regulations to accommodate NELAP requirements, there should be little adverse affect on the harmonization of several regulations within EPA, with FDA or the international GLP community. Due consideration would have to be given to allow the GLP-regulated community to respond to changes made in the regulations or direction of enforcement action s(rule making, comment periods, etc.). Such problem areas as the concerns of the regulated GLP community; the legality of delegation of EPA GLP responsibilities to States; the use of “for-fee” third-party assessors; the establishment of a reasonable fee structure; the archiving, tracking and processing of inspection/assessment data, etc., all should be addressed before this option can be seriously considered.

OPTION 5 - FIFRA/TSCA GLP TESTING FACILITY REGISTRATION

BACKGROUND

One of the difficulties faced by OECA, in addition to not having the staff resources or budget to inspect the estimated 2000 facilities identified as developing data for submission to EPA under GLPs, is that it cannot identify the full universe of testing laboratories. OECA uses OPP and OTS data bases for the laboratory list which is generated from information provided in the final report by the sponsor. The result is a lag time from when the laboratory begins developing data for submission to the time when studies are actually submitted and become

known to EPA and to when these labs are inspected. Each test site in a study is counted as a facility based on information provided in the final report by the sponsor. EPA has data on test facilities but it is incomplete.

One solution EPA has been looking at, to implement the EPA's Office of the Inspector General's (OIG) recommendations, is the mandatory registration of all facilities participating in GLP-regulated studies, based on document submission and assessment.

DESCRIPTION OF OPTION

Facilities which intend to perform FIFRA and TSCA GLP studies for submission to EPA would be required to register their facility with EPA. Facility registration would involve an initial submission of information and documents from the facility for review to establish the basic profile for the facility. Documentation could possibly include: description of size, organization, and capabilities of the facility; the organization, functions, and procedures of the quality assurance unit; general description of instruments and equipment used at the site, and the number and areas of expertise of staff. It might also include current list of standard operating procedures, resumes, CVs and training records of key personnel, floor plans of facility, and a current master schedule. On a periodic schedule, facilities would be required to resubmit certain documents and information.

The Agency or a designated third party contractor would audit the submitted documents. Registration would not confer approval. Facilities with corrected minor deficiencies would be provisionally registered, while facilities with major deficiencies would be targets for inspection. Periodic submission of the facility's master schedule would be required and would provide a means of monitoring work intended for submission to the Agency. This would allow OECA to prioritize its inspections and be able to conduct in-life audit reviews of on-going studies. To remain on the registration list, a submitter would need to continue to remain in GLP compliance verified by an EPA facility inspection audit.

IMPLEMENTATION STRATEGY

A registration fee would be charged which would cover all participants in a study, and would be by facility (sites actually conducting work as part of the study), not by company or corporation. The registration fee, which would require congressional authorization, would be large enough to administer and maintain the registration list and review of document submissions. EPA would have to identify and develop fair criteria standards. After a reasonable period for registration to be implemented, the Agency could reject any studies utilizing unregistered facilities, if the registration system is to succeed.

STRENGTHS

With little effort, a mandatory registration list would provide EPA with a complete database or "known" population of GLP testing facilities. This would meet the OIG's recommendations that the Agency have assurance of a laboratory's awareness of and ability to meet GLP requirements and the provision of an industry-wide laboratory environment more conducive to GLP compliance with the quality of the data remaining high.

In addition, a registration list would provide the Agency with a screening capability and would permit more efficient targeting and use of resources. It would also permit the Agency to make a preliminary assessment of previously uninspected facilities, and utilize limited resources to inspect facilities which appear to have the most serious deficiencies. Assessment of GLP compliance continues to remain with EPA. If EPA were to implement this program, concerns for conflicts of interest and confidentiality would be minimized.

EPA could provide the list of registered GLP laboratories to international governments, which may address international concerns. Additionally, the registration list could be annotated with the dates of EPA facility inspections.

WEAKNESSES

There will be an additional minimal registration cost to the GLP testing facilities to cover administration of the registration list. Registration costs to GLP community may be greater for small companies and companies with multiple testing facilities. In addition, EPA would incur an initial administrative cost to start the program and maintain it. There would be no “value-added” to current GLP compliance for data quality.

On-site evaluations would still be required, and as noted before EPA lacks sufficient resources to adequately inspect all GLP laboratories, but it would be better informed of which labs and which studies were being conducted so it could prioritize its inspections. A “voluntary” registration list would be counter productive because it would not provide the Agency with an “approved” universe of labs.

CONCLUSION

The alternative programs being proposed to help augment the current EPA GLP compliance monitoring system represent a progressive list of options that can be implemented by themselves or in combination with each other. The registration list was not included in the option for the re-evaluation of existing EPA GLP compliance monitoring program with funding considerations, because the group felt, by itself, it would not solve the EPA’s problems with funding and resources for conducting facility site inspections. However, the registration list could prove useful in conjunction with other proposed options.